

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 9/16, 9/20, 38/17, 47/42</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/03451</b> <b>(43) International Publication Date:</b> 28 January 1999 (28.01.99)
<b>(21) International Application Number:</b> PCT/IE97/00049 <b>(22) International Filing Date:</b> 16 July 1997 (16.07.97)  <b>(71) Applicant (for all designated States except US):</b> ANTRIN RE-SEARCH LIMITED [IE/IE]; River Lane, Roscrea, County Tipperary (IE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CORRIGAN, Owen, Ignatius [IE/IE]; 10 Asgard Park, Howth, County Dublin (IE). GUBBINS, Rachel, Helena [IE/IE]; White Lodge, Ennis Road, Limerick (IE). O'DRISCOLL, Caitriona, Mary [IE/IE]; 10 Grosvenor Place, Rathmines, Dublin 6 (IE).  <b>(74) Agent:</b> ANNE RYAN & CO.; 60 Northumberland Road, Ballsbridge, Dublin 4 (IE).		<b>(81) Designated States:</b> AU, BR, CA, CN, CZ, IL, JP, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL FORMULATIONS FOR ORAL ADMINISTRATION  <b>(57) Abstract</b>  Pharmaceutical formulations for oral administration which reduce the local gastrointestinal irritating effects of an active ingredient known to exhibit such effects comprise the active ingredient, for example, a non-steroidal anti-inflammatory drug, dispersed in a milk protein, such as casein or the sodium salt thereof. These formulations are designed to exhibit a cytoprotective effect in the gastrointestinal tract. Controlled release of active ingredient can be achieved with the pharmaceutical formulations if the active ingredient and the milk protein are dispersed in a cellulose ether. The controlled release pharmaceutical formulations exhibit a substantially linear or positively curved release profile.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## Description

### Pharmaceutical formulations for oral administration

#### Technical Field

5 This invention relates to pharmaceutical formulations for oral administration and, in particular, to pharmaceutical formulations containing drugs known to cause gastrointestinal damage or irritation as a negative side effect and which formulations have minimal gastrointestinal irritancy.

#### Background Art

10 A major side effect of certain drugs, including non-steroidal anti-inflammatory agents (NSAIDs), when administered orally is that they cause gastrointestinal irritation (Insel, P.H., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition, 1990, 638-681; Relative safety of oral non-aspirin NSAIDs, Current  
15 Problems in Pharmacovigilance, Vol 20, August 1994). One such NSAID is diclofenac, usually administered as its sodium salt, diclofenac sodium. Diclofenac is usually given two to three times daily for acute therapy in the form of fast acting formulations for an immediate effect. However, for long-term therapy once-daily or twice-daily sustained  
20 release formulations are desirable.

NSAIDs are widely used as therapeutic agents. They are used as general pain killers for short-term therapy and they are also used in the treatment of long-term painful and inflammatory chronic conditions such as rheumatoid arthritis and related conditions. In the former case  
25 immediate, rapid release and absorption are required, whereas in the latter conditions the maintenance of continuous plasma levels is desired. Whether the NSAIDs are used for short-term or long-term therapy their use is likely to be accompanied by gastrointestinal irritation as hereinabove described.

It is known that the gastrointestinal irritation caused by NSAIDs is in part due to local actions of the drugs following ingestion and that the particular dosage form or formulation can significantly affect the nature and intensity of the side effects caused thereby. There is an on-  
5 going and considerable interest in the development of new formulations, for short-term or long-term use, which will lead to an alleviation of these side effects.

Milk is often recommended to be co-administered with NSAIDs to reduce their irritancy.

10 Casein, a milk protein, has been commercially extracted and widely used in industry for most of the 20th century.

Most of the documented pharmaceutical applications of casein are related to its nutritional properties. Thus, it has been used in tonic foods in the treatment of convalescent and under-nourished patients, in  
15 dietary foods and drinks for meal replacement, for weight reduction and in high protein supplements. However, the potential of casein in the pharmaceutical industry is not confined to food uses and there are references in the literature which indicate that casein and caseinates can be used as excipients in dosage forms and as drug carriers.

20 Casein has been included in a slow release preparation containing nifedipine and a material such as magnesium silicate which is enteric coated and encapsulated (Japanese Patent No. 90046008).

It has been reported (Millar, F.C. and Corrigan, O.I. (1991), Drug Dev. Ind. Pharm., 17, 1593-1607) that solid dispersions of highly  
25 crystalline drugs such as chlorothiazide with the phosphoprotein sodium caseinate (NAC) have enhanced dissolution rates. The dissolution characteristics of casein-ibuprofen compacts, over a range of compositions, in phosphate buffer have been investigated. Both the salt (sodium caseinate) and the acid form (acid casein) of the protein  
30 were investigated. The dissolution rate of acid casein was half that of the salt form. The differences observed for the respective forms were

attributed partly to pH differences occurring in the aqueous boundary layers- the pH values being lower in acid casein systems, and partly due to rheological differences. For example, acid casein resulted in more viscous solutions and more rigid gels at a given concentration than sodium caseinate (Millar, F.C. and Corrigan, O.I. (1993), Int. J. Pharmaceutics 92, 97-104).

EP-A 0 282 020 describes pharmaceutical preparations for oral administration in the form of tablets, granules, capsules and dry syrups, which comprise an acidic NSAID having a mean particle size of 100  $\mu\text{m}$  or less, to achieve the desired solubility, and a protein hydrolysate or a polypeptide each having a mean molecular weight of 4,000 - 12,000, which preparations are found to achieve high bioavailability of the NSAID. The NSAIDs are indicated to be of the phenylpropionic acid series such as ibuprofen, of the salicylic acid series such as aspirin or of the anthranilic acid series such as mefenamic acid. Typical protein hydrolysates are those of gelatin and casein i.e. not molecular gelatin or casein.

In EP-A 0 282 020 tablets are indicated to be the most suited form of administration in view of patient compliance and it is also stated that tablets comprising the acidic NSAID, which is absorbed rapidly, are desired. The preparations in addition to exhibiting high bioavailability are also indicated to have a high absorption rate and a reduced oral irritation when administered. This reduced irritation refers to the organoleptic properties of the preparations as illustrated in Table 4 and not local irritation in the gastrointestinal tract. The preparations of EP-A 0 282 020 were developed so as to achieve acidic NSAID preparations having immediate analgesic and antipyretic effects and having decreased side effects when so used.

The preparations of EP-A 0 282 020 because they are fast acting are not appropriate for long-term therapy

There is a requirement for controlled release type products in the case of the long-term use of NSAIDs and other drugs that cause local irritation in the gastrointestinal tract.

5           Controlled/sustained release formulations containing diclofenac sodium compressed with cellulose derivatives, for example, cellulose  
ethers, are known (Vandelli, M.A. *et al.* (April 16-19, 1994, the  
Netherlands) Third European Symposium on Controlled Drug Delivery  
264-268). The cellulose derivatives are used to control the release of  
10       diclofenac sodium. However, the release profiles are non-linear  
showing a continuously declining rate of drug release. Conventional  
diclofenac formulations contain diclofenac in the sodium salt form  
because it is more soluble in this form than the acid form and,  
therefore dissolves more rapidly and is likely to be absorbed quicker  
and more completely. The acid form of the drug is less soluble and  
15       consequently has a greater potential to be incompletely absorbed.  
However, we have demonstrated, as hereinafter described, that the salt  
form of the drug is more irritant to the gastrointestinal tract than the  
acid form.

20           Difene as 100 mg capsules is a trade mark for a diclofenac sodium sustained release pellet drug delivery system marketed by Klinge Pharma and Co.

Sustained release diclofenac sodium tablets (75 mg and 100 mg) are marketed by Geigy Pharmaceuticals under the trade mark Voltarol Retard.

25           In situations where release from a dosage form is the rate determining step controlling the absorption of a drug, then linear drug release profiles, reflecting constant release rate or, indeed, release  
profiles with positive curvatures are most likely to give a constant  
blood level, namely a low peak to trough ratio and also low  
30       concentrations of the released drug in the gastrointestinal tract.

It is an object of the present invention to provide pharmaceutical formulations for oral administration, which exhibit reduced gastrointestinal damage and irritation relative to known formulations.

- 5 It is also an object of the present invention to provide pharmaceutical formulations for oral administration which enable one to achieve an improved drug release profile relative to said known formulations, whereby one can achieve optimal blood levels with minimal gastrointestinal irritation in long-term or short-term therapy.

#### Disclosure of Invention

- 10 Accordingly, the invention provides a pharmaceutical formulation for oral administration which reduces the local gastrointestinal irritating effects of an active ingredient known to exhibit such effects, which comprises said active ingredient dispersed in a milk protein.

- 15 The pharmaceutical formulations according to the invention are designed to exhibit a cytoprotective effect in the gastrointestinal tract.

- By active ingredient herein is meant one or more active ingredients with the indicated gastrointestinal irritating effects. Alternatively, when a mixture of active ingredients is used, it will  
20 suffice that one such active ingredient exhibits gastrointestinal irritating effects.

Preferably, the milk protein has a molecular weight in the range 19,000 - 25,000.

- 25 More particularly, the milk protein is casein or an alkali metal salt thereof. An especially preferred milk protein is sodium caseinate.

Another suitable milk protein constituent is a whey protein comprised of  $\beta$ -lactoglobulin and  $\alpha$ -lactalbumin produced by subjecting pasteurised whey to selective ion exchange. A suitable such whey

protein is one marketed by Bio-Isolates Plc, Swansea, U.K. under the trade name BiPRO (Bio-Isolates Protein). Similar whey proteins are obtainable from An Bórd Baine (The Irish Dairy Board).

5       The invention also provides controlled released pharmaceutical formulations for oral administration, wherein the active ingredient and the milk protein as herein defined are dispersed in a cellulose ether.

10       The controlled release pharmaceutical formulations according to the invention give an improved drug release profile relative to conventional controlled/sustained formulations, in particular NSAID formulations, so as to provide formulations for once- or twice-daily administration.

      The cellulose ether is suitably a hydroxypropylmethylcellulose (HPMC).

15       Especially suitable cellulose ethers are those sold under the trade mark METHOCEL, especially those complying with USP 2208 and USP 2910. An example of such a cellulose ether is METHOCEL K100LV, a 2% aqueous solution of which has a nominal viscosity of the order of 100 cps.

20       However, the type and amount of HPMC used is dependent on a number of factors, including the drug, the dose and the type of delivery system used.

      The active ingredient is suitably an NSAID.

25       The NSAID is any NSAID which has the disadvantages set out above. However, the invention will be described hereinafter with respect to two NSAIDs, namely diclofenac or the sodium salt thereof and ibuprofen (Example 6).

      Studies have been carried out by us which show that the acid form of diclofenac seems to have a less irritant effect on the



gastrointestinal tract than the sodium salt using the rabbit colonic method; consistent with the findings of Fara, J.W. and Myrback, R.E., ((1990); Pharm.Res., 7, 616). We have observed in our studies in rabbits that the inclusion of solid sodium caseinate with diclofenac can  
5 reduce the relative irritancy of diclofenac containing products *versus* controls as hereinafter described in Example 4.

We have also observed in studies in rats that diclofenac increases the apparent permeability of the absorption marker polyethylene glycol (PEG), an effect consistent with membrane damage and irritancy.  
10 However, the presence of sodium caseinate in formulations in accordance with the invention eliminates this permeability enhancement, without affecting the absorption of drug, as hereinafter described in Example 5.

The controlled release formulation according to the invention  
15 can take various forms, provided that it exhibits a substantially linear or positively curved release profile of the active ingredient and confers a cytoprotective effect in the gastrointestinal tract.

The pharmaceutical formulation according to the invention can take many forms.

20 Thus, the formulations according to the invention can be in the form of single matrix units such as tablets or matrix-type granules, namely multiparticulate formulations. Such formulation types are known *per se*. These formulations can be prepared generally by mixing and compression, granulation processes, which may require  
25 additional conventional excipients essential for the granulation process, spray drying or freeze drying the components together. Polyphase particulates are packed into capsules or compressed with suitable auxiliary agents into disintegrating tablets which release the matrix granules. The multiparticulate formulations according to the invention  
30 may be formulated as reconstitutable powders or granulates for suspension prior to administration or they may be formulated as non-aqueous suspensions.

Other suitable dosage forms include, for example, soft gelatin capsules.

It will be appreciated that the pharmaceutical formulations according to the invention can also be formulated as rectal delivery systems.

In our studies, sodium caseinate systems gave the best shaped release profiles. Although not wishing to be bound by any theoretical explanation of any aspect of the invention, it is postulated that the sodium salt of casein gives a local solubility enhancing effect and/or buffering effect within and in the vicinity of the dosage form as the dosage form takes up the dissolution medium. The caseinate may also influence the hydration rate, pore structure or gel structure of the matrix in a manner appropriate for linear release. Milk proteins of the casein type have a unique ability to form high molecular aggregates with slower diffusion in solution. Accordingly, this ability may be involved in influencing or controlling drug release from the formulation matrices. Such aggregates or micelles would be destroyed by enzyme hydrolysis and would not be a feature of casein hydrolysates of the type described in EP-A 0 282 020 described above. The molecular components of casein have molecular weights in the range 19,000 - 25,000, while the molecular weights of the hydrated casein micelles are much larger (McMahon, D.J., and Brown, R.J., (1984); Journal of Dairy Science, 67 499).

#### Brief Description of Drawings

Fig. 1 is a graph of dissolution (%) *versus* time (min.) for a formulation according to the present invention prepared in accordance with Example 1 relative to two conventional sustained release formulations;

Fig. 2 is a graph of dissolution (%) *versus* time (min.) for a formulation according to the present invention prepared in

accordance with Example 2 relative to a formulation containing no milk protein;

Fig. 3 is a graph of dissolution (%) *versus* time (min.) for formulations according to the present invention prepared in accordance with Examples 1 and 3;

Fig. 4 is a graph of the ratio of test irritation score to corresponding control irritation score for a number of formulations described in Example 4; and

Fig. 5 illustrates the effect of diclofenac and sodium caseinate on the apparent permeability coefficient of PEG 4000 through the rat intestinal mucosa as described in Example 5.

#### Modes for Carrying Out the Invention

The invention will be further illustrated with reference to the accompanying Examples.

#### Example 1

A sustained release unit matrix dosage form of diclofenac (acid) exhibiting a controlled release of diclofenac over a five hour period was prepared from the following ingredients in the indicated proportions:

<u>Ingredient</u>	<u>Proportion %</u>
Diclofenac acid	50.000
Sodium caseinate	24.375
HPMC K100LV	24.375
Magnesium stearate	1.250

Discs prepared from the above ingredients containing 100 mg of drug were compressed directly using 1.3 cm diameter punches. The diclofenac (acid) was obtained from Heumann Pharma GmbH,

Nuremberg, Germany and the sodium caseinate was obtained from An Bórd Baine (The Irish Dairy Board).

The dissolution of the discs thereby prepared was determined according to the Paddle Method of U.S. Pharmacopoeia XXIII (USP XXIII) in 500 ml phosphate buffer at pH 7.3. and 100 r.p.m. and compared with the sustained release diclofenac sodium products sold under the trade marks Difene S.R. and Voltarol Retard. The results are indicated in Fig. 1. In Fig. 1 curve a) represents the formulation according to the invention, curve b) represents Difene S.R. (100 mg); and curve c) represents Voltarol Retard (100 mg).

It will be evident from Fig. 1 that a much more constant release was obtained for the formulation in accordance with the invention relative to the commercial products studied.

#### Example 2

Example 1 was repeated except that the HPMC used was HPMC K15M. The discs -discs "X" so prepared were compared with discs -discs "Y" having the following composition:

	<u>Ingredient</u>	<u>Proportion %</u>
	Diclofenac acid	50.00
	HPMC K15M	48.75
	Magnesium stearate	1.25

The results are indicated in Fig. 2. In Fig. 2 curve a) represents discs X and curve b) represents discs Y.

It will be observed that a more constant and linear release was obtained for the formulation in accordance with the invention relative to discs Y which lack sodium caseinate. Beyond 100 min., the curve for formulation X curves upwards indicating an increase in release rate in contrast to formulation Y which curves downwards indicating a decreasing rate of drug release.

### Example 3

Example 1 was repeated so as to prepare discs having the following composition:

	<u>Ingredient</u>	<u>Proportion %</u>
5	Diclofenac acid	33.33
	Sodium caseinate	32.50
	HPMC K100LV	32.50
	Magnesium stearate	1.66

10 The discs so prepared containing 100 mg of active ingredient were compared with the discs prepared in Example 1. The results are indicated in Fig. 3. In Fig. 3 curve a) represents the formulation of Example 1 and curve b) represents the formulation of the present Example.

15 It will be observed that in each case a constant, substantially linear release of active ingredient was obtained, release being more delayed with the inclusion of greater amounts of sodium caseinate and HPMC relative to diclofenac.

### Example 4

20 Fara, J.W. *et al.* ((1988) Pharm. Res. 5, 165-171) have compared the Carlborg-Densert cat oesophagus model (Carlborg, B., and Densert, O., (1980); Eur. Surg. Res. 12: 270-282), the Alphin Droppleman cat gastric mucosa model (Alphin, R.S., and Droppleman, D.A., (1971); J.Pharm. Sci., 60: 1314-1316) adapted for dog intestine and the same model adapted for the rabbit colon. These authors found  
25 the rabbit colon model to be a sensitive and reproducible means for evaluating the topical effect of up to three substances simultaneously applied to the colonic mucosa.

This model involves exposure of the *in situ* colonic mucosa to drugs for a fixed period of time with subsequent macroscopic and histological examination.

5 The macroscopic and histological effects are scored on four and eight point scales, respectively.

We have carried out an experiment on rabbit colon based on the method of Fara, J.W., *et al.* (1988)(*supra*) in which we investigated the disc product prepared according to Example 1, a product containing diclofenac 10% in a 20% gel in sodium caseinate and the Klucel system  
10 of Fara, J.W. and Myrback, R.E. (1990)(*supra*).

The results obtained are summarised in Fig. 4, where the irritation score ratio (test/control) for formulations containing either the acid or salt form of diclofenac are presented. When compared by the method of Fara, J.W. and Myrback, R.E. (1990)(*supra*) (i.e. the  
15 Klucel system) a significant difference in irritation was observed; the acid form of the drug showing less irritation than the sodium salt form. A similar trend is evident in the sodium caseinate containing products i.e. the gel product (containing sodium caseinate as a 20% gel) and the disc product prepared according to Example 1.

#### 20 Example 5

The intestinal permeability marker, PEG 4000, was perfused through the rat intestine using the single pass perfusion method (Komiya, I., *et al* (1980); Int. J.Pharm., 4, 249-262). The effect of diclofenac in the presence or absence of sodium caseinate on the  
25 apparent permeability coefficient of the marker is shown in Fig. 5. Diclofenac alone increased the permeability of the marker, whereas in the presence of sodium caseinate the permeability coefficient of the marker decreased. The significant reduction of the steady state marker permeability coefficient ( $p < 0.05$ ) on inclusion of sodium caseinate is  
30 consistent with a cytoprotective effect.

Example 6

5 A study was carried out to compare the dissolution of the NSAID ibuprofen in combination with either a caseinate hydrolysate as in the case of EP-A 0 282 020 or sodium caseinate in accordance with the invention. It was found that the release of ibuprofen from the casein hydrolysate was much faster than the release of ibuprofen from sodium caseinate, particularly in the initial stages of the release as shown in Table 1.

Table 1

System	Time (min) for % Release		
	5%	50%	95%
ibuprofen: sodium caseinate	6	23	55
ibuprofen: casein hydrolysate	0.5	3.25	18.5

10 Accordingly, it took 23 min. for 50% release from the sodium caseinate system, but only 3.25 min. in the case of casein hydrolysate, namely a seven fold difference in 'rate'. The inclusion of hydroxypropylmethylcellulose in the formulation according to the invention further reduces the rate of release.

Claims:-

1. A pharmaceutical formulation for oral administration which reduces the local gastrointestinal irritating effects of an active ingredient known to exhibit such effects, which comprises said active ingredient dispersed in a milk protein.  
5
2. A pharmaceutical formulation according to Claim 1, wherein the milk protein has a molecular weight in the range 19,000 - 25,000.
3. A pharmaceutical formulation according to Claim 1 or 2, wherein the milk protein is casein or an alkali metal salt thereof.  
10
4. A pharmaceutical formulation according to Claim 3, wherein the protein is sodium caseinate.
5. A pharmaceutical formulation according to any preceding claim, wherein the active ingredient and the milk protein are dispersed in a cellulose ether.  
15
6. A pharmaceutical formulation according to Claim 5, wherein the cellulose ether is a hydroxypropylmethylcellulose.
7. A pharmaceutical formulation according to Claim 6, wherein a 2% aqueous solution of the hydroxypropylmethylcellulose has a nominal viscosity of the order of 100 cps.  
20
8. A pharmaceutical formulation according to any one of Claims 5-7, which exhibits a substantially linear release profile of the active ingredient.
9. A pharmaceutical formulation according to any preceding claim, wherein the active ingredient is a non-steroidal anti-inflammatory drug (NSAID).  
25



10. A pharmaceutical formulation according to Claim 9, wherein the NSAID is diclofenac or the sodium salt thereof.

11. A pharmaceutical formulation according to any preceding claim, which is in the form of a single matrix unit.

5 12. A pharmaceutical formulation according to any one of Claims 1-10, which is in the form of matrix-type granules.

13. A pharmaceutical formulation according to any one of Claims 1-10, which is in the form of a powder or granulate.

10 14. A pharmaceutical formulation according to any preceding claim, which contains one or more auxiliary agent(s).

15. A pharmaceutical formulation according to Claim 1, substantially as hereinbefore described and exemplified.

1/5

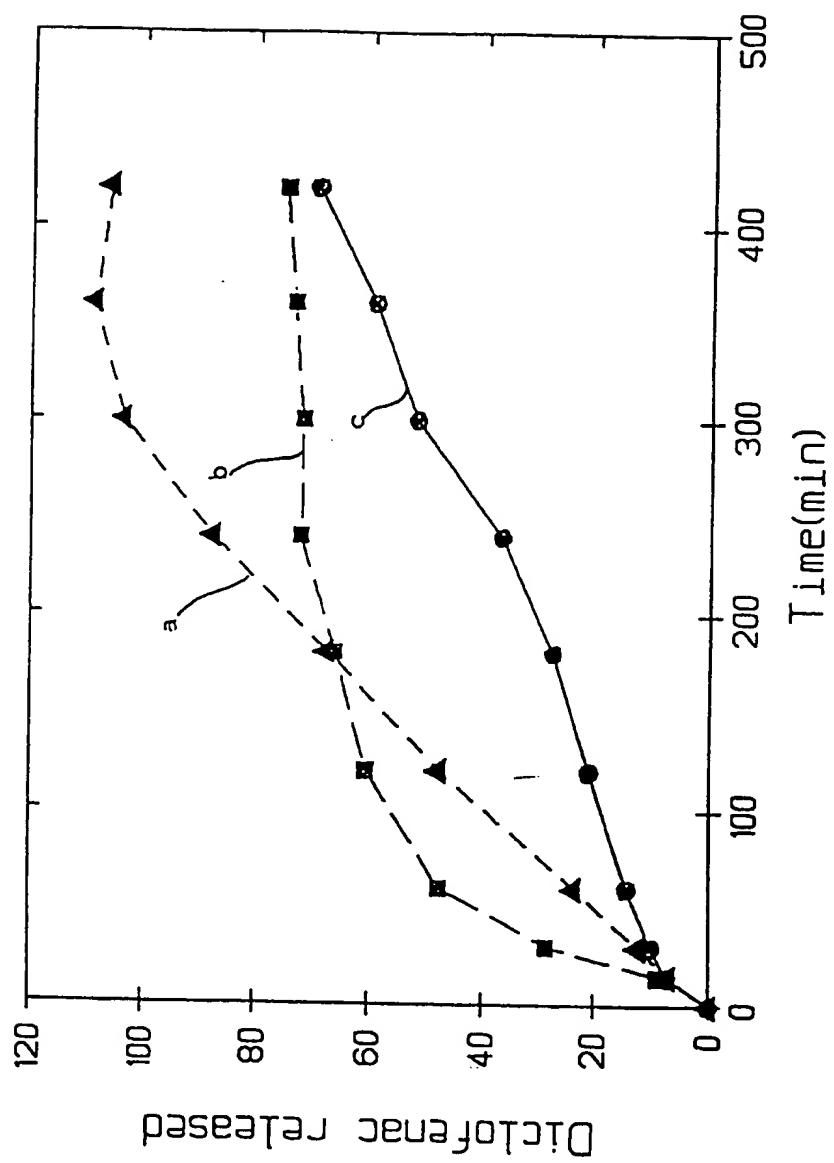


FIG. 1

2/5

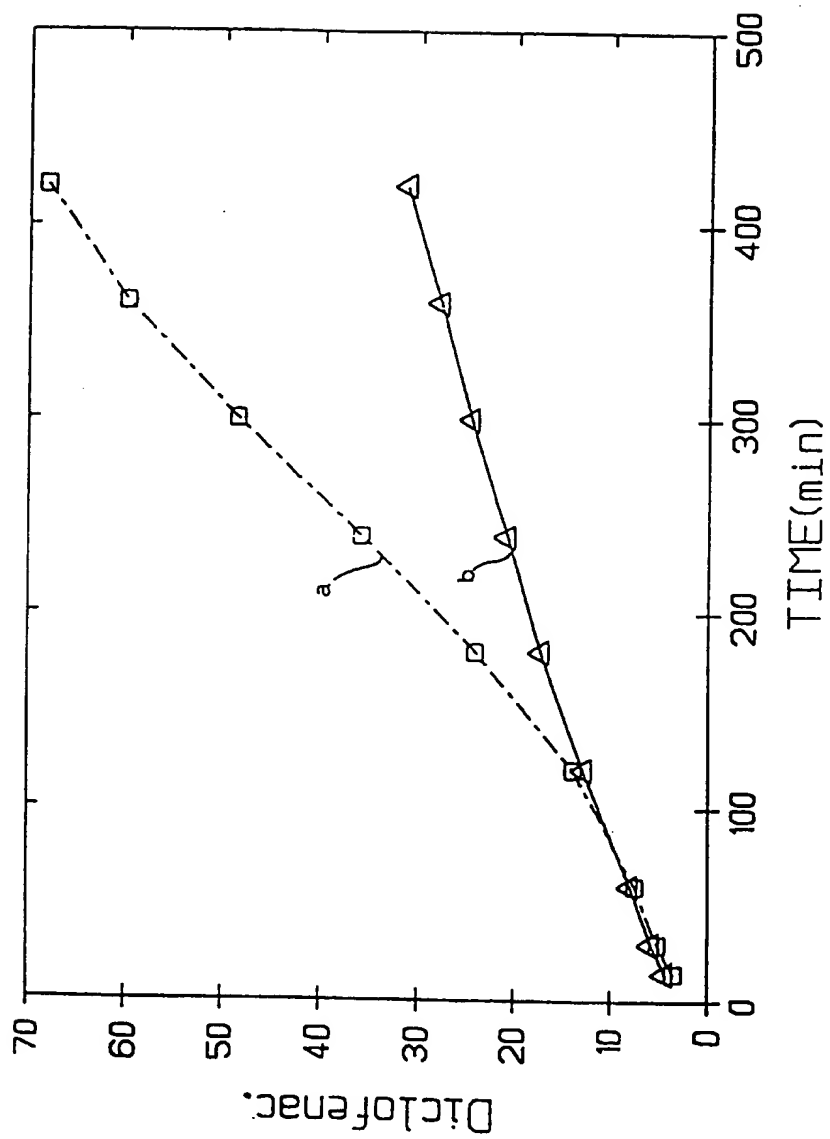


FIG. 2

3/5

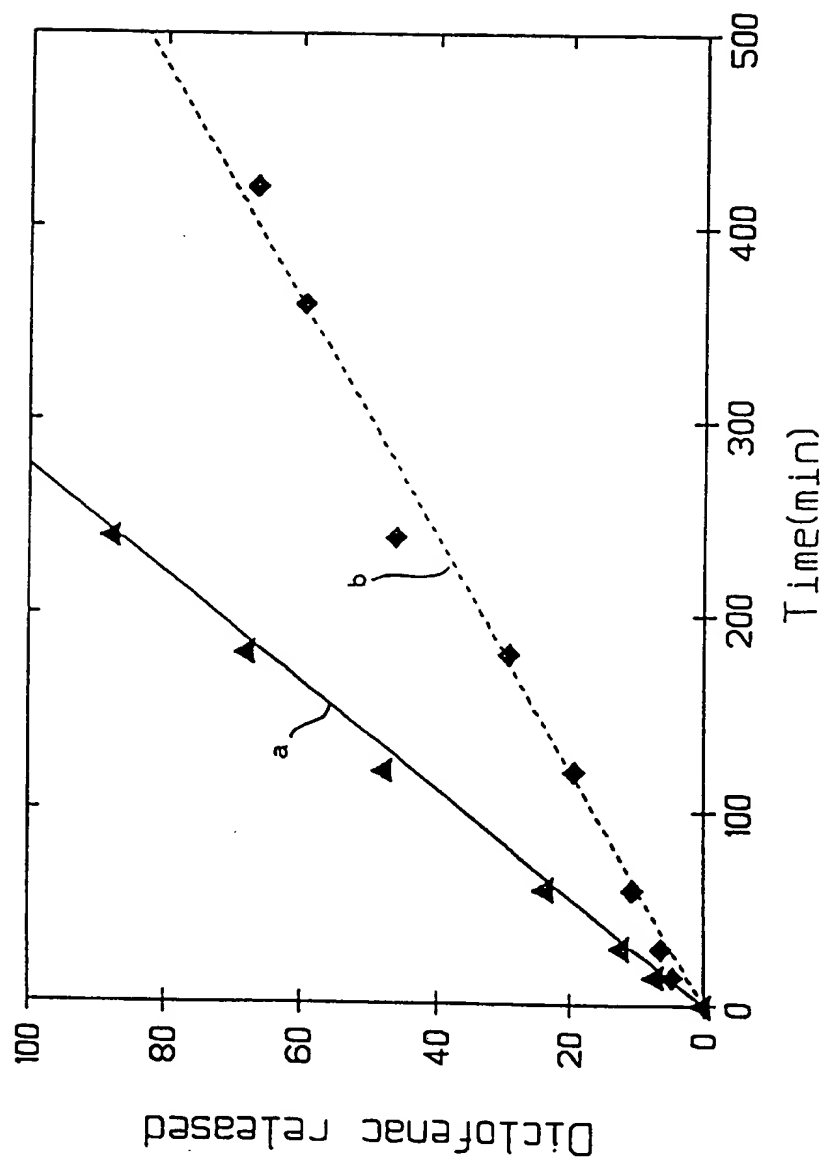


FIG. 3

4/5

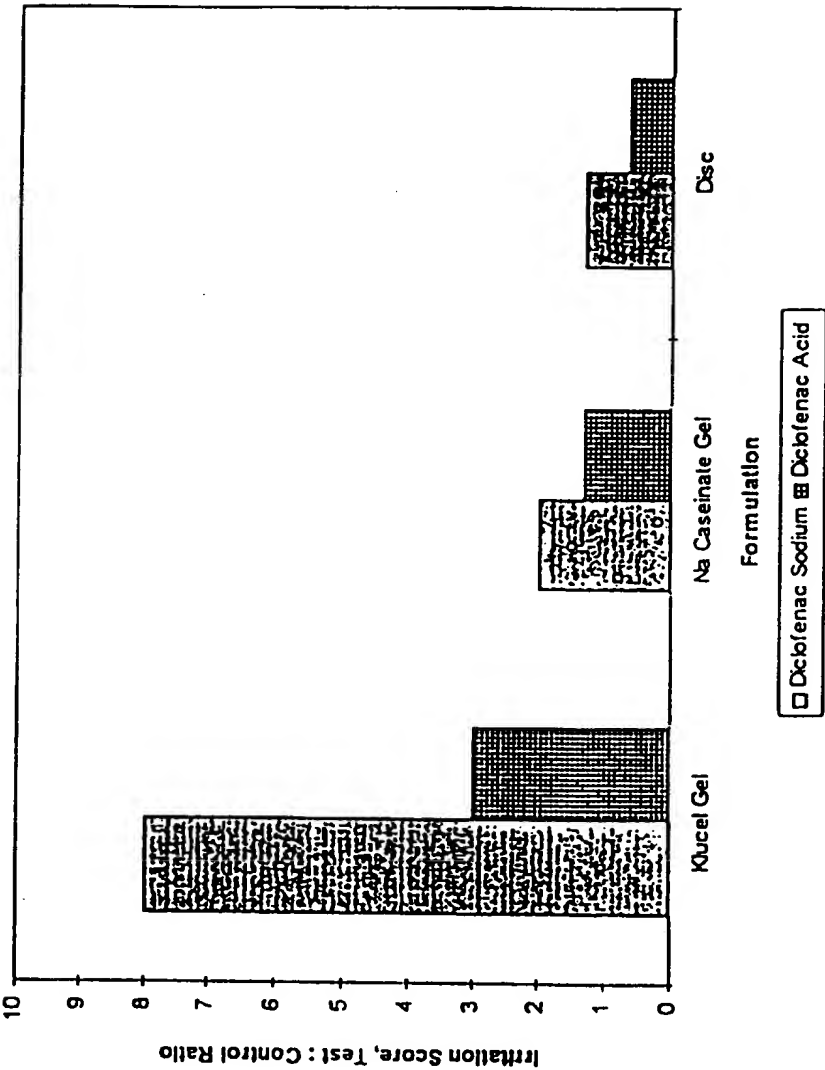


FIG. 4

5/5

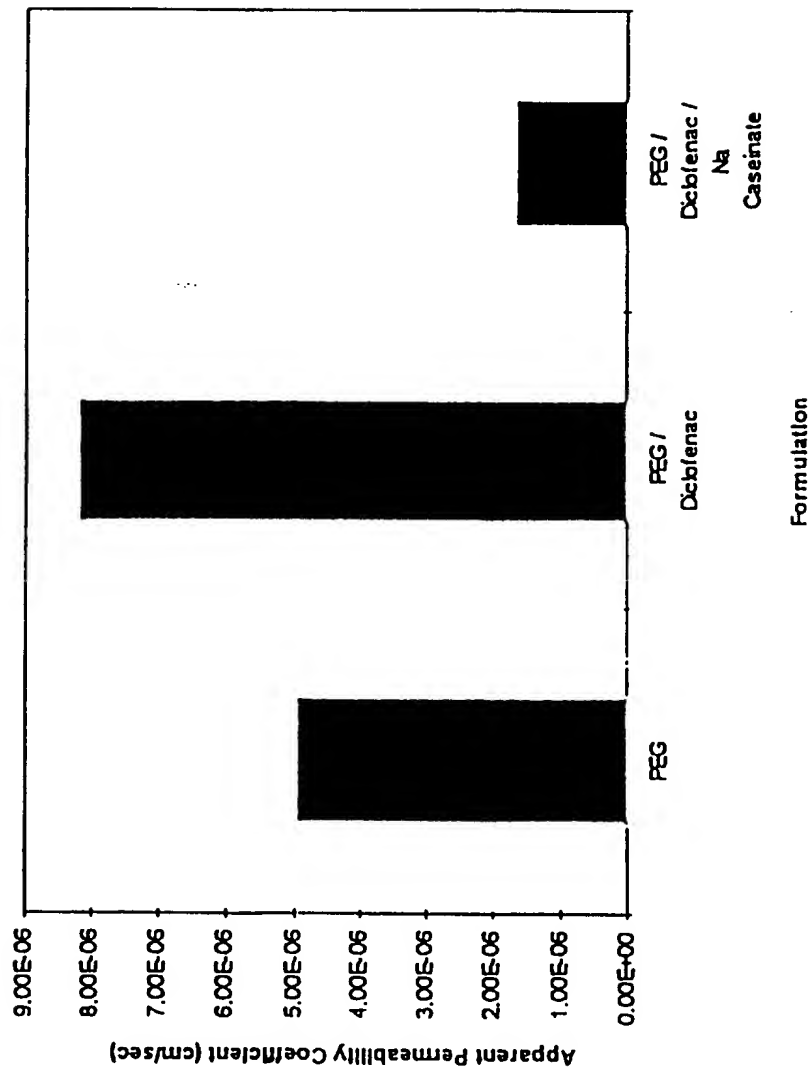


FIG. 5

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 97/00049

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/16 A61K9/20 A61K38/17 A61K47/42

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 326 618 A (NIPPON HYPOX LABORATORIES) 9 August 1989 see page 5, column 14 see page 5, line 22 - line 27 see page 13, line 25 - page 14, line 14 see page 15; table 1 see page 23 - page 24; examples 23-25 see page 26; example 29 see page 28, line 13 - line 22	1,2,5,9, 10,13-15
Y	---	3,4,6,8, 11,12
Y	EP 0 699 444 A (DALHOUSIE UNIVERSITY) 6 March 1996 see page 3, line 12 - line 14 see page 3, line 18 - line 19 see page 4, line 34 - line 38 ---	3,4
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

6 March 1998

Date of mailing of the international search report

24.04.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Alvarez Alvarez, C

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 97/00049

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 24188 A (HEXAL PHARMA GMBH ET AL.) 14 September 1995 see claims 1-5; figure 1; examples 1-3 ---	6,8,11, 12
X	EP 0 361 348 A (NIPPON HYPOX LABORATORIES INC.) 4 April 1990 see abstract; claims 1,2 ---	1,2
X	EP 0 582 186 A (MERZ + CO. GMBH & CO.) 9 February 1994 see page 2, line 48 - page 3, line 7 see page 3, line 33 see page 3, line 27 - line 29 see examples 3,4 ---	1-4,9, 11-15
A	EP 0 715 857 A (RHONE-POULENC RORER GMBH) 12 June 1996 see page 3, line 28 - line 29 see page 3, line 58 - page 4, line 2 see page 4, line 30 - line 33 see claims 1,6,7,11,13,14 ---	1-6,9-16
A	EP 0 282 020 A (NISSHIN FLOUR MILLING CO. LTD.) 14 September 1988 cited in the application see the whole document ---	1,5,9-15
A	DATABASE WPI Week 9124 Derwent Publications Ltd., London, GB; AN 91-175119 XP002057963 & JP 03 106 828 A (SNOW BRAND MILK PROD. CO. LTD.) , 7 May 1991 see abstract -----	1



# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IE 97/00049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 326618 A	09-08-89	JP 2654445 B	17-09-97
		JP 63215642 A	08-09-88
		JP 63215640 A	08-09-88
		DK 617088 A	04-11-88
		WO 8806457 A	07-09-88
		US 5051406 A	24-09-91
-----			
EP 699444 A	06-03-96	US 5578576 A	26-11-96
		AU 3040795 A	14-03-96
		JP 8188536 A	23-07-96
-----			
WO 9524188 A	14-09-95	DE 4408326 A	14-09-95
		AU 2069595 A	25-09-95
		EP 0749304 A	27-12-96
		FI 963567 A	10-09-96
		JP 9509953 T	07-10-97
		NO 963796 A	06-11-96
		PL 316196 A	23-12-96
-----			
EP 361348 A	04-04-90	JP 2088522 A	28-03-90
-----			
EP 582186 A	09-02-94	DE 4225730 A	10-02-94
		AU 669731 B	20-06-96
		AU 4706993 A	03-03-94
		CA 2141691 A	17-02-94
		CN 1086708 A	18-05-94
		WO 9403158 A	17-02-94
		JP 7509479 T	19-10-95
		LT 3201 B	27-03-95
		LV 10182 A,B	20-10-94
		MX 9304675 A	31-03-94
		US 5382601 A	17-01-95
		ZA 9305614 A	03-02-95
-----			
EP 715857 A	12-06-96	DE 4444051 A	13-06-96
		AU 3794595 A	20-06-96
		CA 2164777 A	11-06-96
		JP 8208520 A	13-08-96
		ZA 9510427 A	18-06-96
-----			

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/IE 97/00049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 282020 A	14-09-88	JP 1203335 A	16-08-89
		JP 2034064 C	19-03-96
		JP 7068120 B	26-07-95
		JP 63218618 A	12-09-88
		CA 1324083 A	09-11-93
		DE 3882157 A	12-08-93
		DE 3882157 T	11-11-93
		KR 9616204 B	06-12-96
		US 5080907 A	14-01-92
-----			